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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,863	07/21/2006	Tiberio Bruzzese	10165-7	1570

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,863	BRUZZESE, TIBERIO	
	Examiner	Art Unit	
	JENNIFER M. KIM	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 24, 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-49* is/are pending in the application.

4a) Of the above claim(s) *32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-31 and 34-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed September 24, 2010 have been received and entered into the application.

Response to Arguments

Applicant's arguments filed September 24, 2010 have been fully considered but they are not persuasive. Applicant argues that the prior art requires that GLA is an essential feature of a composition for treating schizophrenia, yet the presently claimed method that alleviates schizophrenia symptoms in animal involves a composition that does not include GLA. This is not persuasive because it is noted that the present invention is drawn to the transition term “comprising” which is synonymous with “including," “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or steps. Further, Horrobin provide capsules containing EPA and DHA for the treatment of schizophrenia in their example A1 (see column 6, lines 45-50).

Applicant argues that Nishikawa et al. is related to the treatment of psychosis in general not to schizophrenia specifically as present in claim 29, and that psychosis is distinct from schizophrenia as established in Merck Manual. This is not persuasive because the treatment of schizophrenia as a species of psychosis is clearly named by Nishikawa et al. (see examples, column 1). The treatment of psychosis in general does

not negate the fact that the schizophrenia as a specific condition of psychosis claimed was specifically taught. The Merck Manual has been carefully reviewed. However, Applicant's attention is drawn to the very first sentence on page 1 which states that schizophrenia is a mental disorder characterized by loss of contact with reality **(psychosis).**

Applicant argues that the Nishikawa et al's major concern is the purification but not a concentration. This is not persuasive because Nishikawa et al. teaches usefulness of DHA in the treatment of schizophrenia while Horrobin provides capsules containing EPA and DHA and the effective amounts for the treatment of schizophrenia in their example A1 (see column 6, lines 45-50). Furthermore, no unobviousness is seen in the concentration claimed because once the usefulness of a compound and their therapeutic amounts are known to treat a condition, it is within the skill of the artisan to determine the optimum concentration from the known therapeutic amounts.

Applicant argues that 1.132 Declaration and the example 6 of the present application demonstrated that the composition according to the present invention can counteract the induced schizophreniform psychosis. The Declaration and the Examples have been carefully reviewed and considered. However, they are not persuasive because the fact that the teaching and the example from Horrobin that the combination of DHA and EPA for the treatment of schizophrenia was known at the time the invention was made. Moreover, Applicants are reminded that when relying on comparative testing, the applicant is under a duty to compare his claimed invention with the closest prior art (i.e. Horrobin et al. U.S. 4,977,187). See, In re Burckel, 592 F.2d 1175, 201

USPQ 67 (CCPA 1979); In re Merchant, 575 F.2d 865, 197 USPQ 785 (CCPA 1978); Ex parte Beck, 9 USPQ 2d 2000, 2002 (Bd. Pat. App. & Int. 1987) ("comparative evidence, to be effective, must compare the claimed subject matter with the closest prior art"); Ex parte Meyer, 6 USPQ2d 1966, 1968 (Bd. Pat. App. & Int. 1988) ("An applicant relying upon a comparative showing to rebut a prima facie case of obviousness must compare his claimed invention with the closet prior art."). However, the amounts of active agents to be used, optimization of the concentration, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Applicant argues that the present invention provides a treatment of schizophrenia, based on a composition that acts through a mechanism of affinity towards the NMDA receptors, other than the more traditional D2 receptors for dopamine, and is strongly active on the positive symptoms and perfectly tolerated and free of the side effects of all the known anti-psychotic/neuroleptic drugs. Further, the claim 30 and 31 are amended to recite the positive symptoms of schizophrenia. This is not persuasive because Nishikawa et al. teach that there is a need for a drug which can improve not only positive symptoms of schizophrenia but also its negative symptoms which causes no side effect while Horrobin disclosed examples comprising capsules containing EPA and DHA and the effective amounts for the treatment of schizophrenia in their example A1 (see column 6, lines 45-50). Accordingly, disclosed examples and preferred embodiments in Nishikawa et al. in improvements in negative symptoms of

schizophrenia do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 169 USPQ 423 (CCPA 1971). The mere fact that the preferred embodiment is a treatment of negative symptoms does not teach away from the broad disclosure which discloses, as indicated above that Nishizawa et al. teaches that their composition is effective in the treatment of schizophrenia includes both positive and negative symptoms.

Applicant argues that Nishikawa et al. teaches that DHA can be formulated as capsules but the present application recited that the drug is in the form of soft gelatin capsules in pure form but Nishikawa et al's composition contains numerous organic and inorganic carriers and diluents in various weight ratios. This is not persuasive because no unobviousness is seen in the pharmaceutical forms, e.g. capsules or soft gelatin capsules without impurities since they are deem obvious variations to skilled pharmacologist and routine practice to manufacture a product without impurities.

Applicant argues that Nishikawa et al. is not an enabling reference with respect to use of ethyl esters of DHA because ethyl esters of DHA are neither claimed nor mentioned in the examples of Nishikawa et al.; and therefore, would not motivate one skilled in the art to use the ethyl esters of DHA in a formulation for treating schizophrenia. This is not persuasive because Nishikawa et al. teach that ethyl esters can be employed in as derivatives while Horrobin provides capsules containing EPA and DHA and the effective amounts for the treatment of schizophrenia in their example A1 (see column 6, lines 45-50). Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made,

because every element of the invention has been collectively taught by the combined teachings of the references.

Applicant argues that all the scientific works published after the publications of Nishikawa et al, in 1992 have lead to the progressive acknowledgement that other omega-3 acids, particularly EPA, were definitely superior in activity with respect to DHA. Applicant cites Mellor et al, Horrobin '568 patent and Peet '077 patent. This is not persuasive because the teaching that EPA may be superior than DHA does not change the teaching of Nishikawa et al. that DHA is effective for the treatment of schizophrenia and that combination of EPA and DHA was known at the time the invention was made for the treatment of schizophrenia in view of Horrobin.

Applicant argues that Horrobin (U.S.Patent No. 4,977,187) discloses that the presence of GLA (which is an omega-6 acid) is an essential feature, therefore, the absence of GA from the presently claimed composition is unexpected and non-obvious. This is not persuasive because Applicant's attention is drawn to illustrated example of Horrobin on column 6, under A. wherein it illustrates capsules containing EPA and DHA for the treatment of schizophrenia. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

2. Claims 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a method of using a composition for the preparation of a drug for . . . .**treatment** of psychiatric disturbances", does not reasonably provide enablement for "administration of at least another drug effective for **preventing** …the disturbances of CNS". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: the nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

> ***Nature of the Invention*:** All of the rejected claims are drawn to a method of using a composition for the preparation of a drug for the treatment of the psychiatric disturbances of the central nervous system (CNS) selected from the group consisting of schizophrenia comprising a component selected from the group consisting of DHA in admixture with eicosapentaenoic acid (EPA, C20:5 n-3), in a ratio of 1:0.5 to 1:1.7, respectively, and/or the pharmaceutically acceptable derivatives and/or precursors thereof; wherein said component is

present in a concentration not lower than 70% by weight of the total fatty acids weight in the composition with the proviso that it does not comprise 10 to 40% by weight of reducing/antioxidant vitamins or provitamins with at least another drug effective for the **prevention** of the disturbances of CNS. The nature of the invention is extremely complex in that it encompasses administration of a drug that has an **actual effect in preventing** CNS disturbances (i.e. schizophrenia) such that the subject treated with the above compounds does not contract schizophrenia.

Breath of the Claims: The complex of nature of the claims is greatly exacerbated by breath of the claims. The claims encompass **prevention** of a disorder that is understand very little in terms of specific etiology.

Guidance of the Specification: The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually **prevent** schizophrenia is minimal. All of the guidance provided by the specification is directed towards **treatment** of schizophrenia rather than the **prevention.**

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of schizophrenia.

State of the Art: While the state of the art is relatively high with regard to treatment of psychological dysfunction (i.e. depression, anxiety, schizophrenia), the state of the art with regard to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or

teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of schizophrenia.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of schizophrenia in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of **prevention** of schizophrenia.

The amount of Experimentation Necessary: In order to practice the claimed invention, one skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and an appropriate animal model system for one of the claimed compounds and then test the combination in the model system to determine whether or not the combination is effective for **prevention** of schizophrenia. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of schizophrenia with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification or any prior art regarding prevention of schizophrenia with compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable

experimentation to practice the claimed invention to prevent the development of schizophrenia in a subject by administration of one of the claimed compounds.

Therefore, a method of using a composition for the preparation of a drug for the treatment of the psychiatric disturbances of the central nervous system (CNS) selected from the group consisting of schizophrenia comprising a component selected from the group consisting of DHA in admixture with eicosapentaenoic acid (EPA, C20:5 n-3), in a ratio of 1:0.5 to 1:1.7, respectively, and/or the pharmaceutically acceptable derivatives and/or precursors thereof; wherein said component is present in a concentration not lower than 70% by weight of the total fatty acids weight in the composition with the proviso that it does not comprise 10 to 40% by weight of reducing/antioxidant vitamins or provitamins with at least another drug effective for the **prevention** of the disturbances of CNS is **not** considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 29-31 and 34-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishikawa et al. (U.S.Patent No. 6,306,907B1) and Horrobin (U.S.Patent No. 4,977,187) and further in view of Chen (U.S.Patent No. 6,759,435 B1).

Nishikawa et al. teaches an oral antipsychotic comprising at least one of docosahexaenoic acid or derivatives thereof as an active ingredient for treatment of psychosis such as schizophrenia. Nishikawa et al. teaches that such antipsychotic is highly safe and effective and can be formulated as capsules (abstract, column 2, lines 55-63). Nishikawa et al. teach that ethyl esters of docosahexaenoic acids can be employed as derivatives (column 2, lines 21-30). Nishikawa et al. teaches that for the oral administration the clinical dose of the active ingredient is preferably from 300mg to 1800 mg per day for adult subjects and can be administered once a day, or twice or three times a day at suitable intervals. (column 3, lines 25-33). Nishikawa et al. teach that the antipsychotic can be suitably administered together with the other suitable antipsychotics, for example haloperidol (column 3, lines 10-15). Nishikawa et al. teach that schizophrenia and its symptoms can be classified into two types, positive symptoms such as hallucinations, delusions, and abnormal behaviors and negative symptoms such as catatonia, autism, and non-emphasis. Nishikawa et al. teach that there is a need for a drug which can improve not only positive symptoms of schizophrenia but also its negative symptoms which causes no side effect. (column 1,

lines 10-30). Nishizawa et al. exemplify that the antipsychotic of DHA showed improvements in negative symptoms of schizophrenia (example 2).

Horrobin exemplifies a capsule containing 200mg purified GLA (gamma linolenic acid: n-6) and 200mg purified EPA for treatment of schizophrenia, 2 to 8 capsules to be taken per day. It is noted that the daily dosage of EPA ranges 400mg to 1600mg per day. (column 6 example A, 2). Horrobin teaches that in the treatment of schizophrenia, composition can be formulated with or **without vitamin E** (column 4, lines 13-25).

Chen teaches that the term schizophrenia encompasses paranoid, disorganized, catatonic, and undifferentiated schizophrenia. (column 7 line 65 to column 8 line 5).

The claims differ from the cited references in claiming combination of DHA and EPA and GLA composition of Horrobin to treat schizophrenia. To employ combinations of DHA and EPA & GLA (gamma-linolenic acid: n-6 essential fatty acid) composition to treat schizophrenia would have been obvious because all the components are well known individually for treating schizophrenia. It would be expected that the combination of components would schizophrenic conditions as well. One of ordinary skill in the art would have combined the antischizophrenic agents by known methods and that in combination, each element merely would have performed the same antischizophrenic activity as it did separately. The convenience of putting the compounds having the same antischizophrenic activity of DHA and EPA & GLA composition together in one dosage form, though perhaps a matter of great convenience does not produce a "new" or "different" function and to those skilled in the art, the use of the old elements in combination would have been obvious. The

motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). The ratio of DHA in admixture with EPA set forth in claims 29 and 34, the dosages set forth in claims 45-47, and the concentration of DHA and EPA by weight of the total fatty acids weight in the composition set forth in claims 35-37 are noted however, the ratio is within the therapeutic amount of each of the agents for the treatment of schizophrenia in the obvious combination. Further, no unobviousness is seen in the concentrations claimed because once the usefulness of a compound is known to treat a condition, it is within the skill of the artisan to determine the optimum concentration. The formulation of soft gelatin capsules set forth in claim 44 is noted, however, such is obvious because both cited reference teach that the active agents can be formulated in capsules in general. Therefore, the soft gelatin capsule would be an obvious variation of capsules form taught by the prior art without a surprising and unexpected result. With regard to the specific schizophrenia to be treated set forth in claim 31, such is obvious because cited references teach the treatment of schizophrenia in general which generally encompasses paranoid, catatonic, disorganized or undifferentiated schizophrenia is well known in the art in view of Chen. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
December 3, 2010